
Disruption of Cerebrospinal Fluid Flow through the Olfactory System May Contribute to Alzheimer's Disease Pathogenesis.

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Public Summary:

Loss of smell, or olfactory dysfunction, is a common occurrence in people who go on to develop Alzheimer's disease. Here I explain how the olfactory system plays a key role in clearing Alzheimer's-related toxins from regions of the brain affected early in Alzheimer's disease. I hypothesize that dysfunction of this clearance route facilitates the accumulation of those toxins, eventually leading to the appearance of classic pathological features of the disease, including plaques and tangles.

Scientific Abstract:

Plaques and tangles may be manifestations of a more substantial underlying cause of Alzheimer's disease (AD). Disease-related changes in the clearance of amyloid-beta (Abeta) and other metabolites suggest this cause may involve cerebrospinal fluid (CSF) flow through the interstitial spaces of the brain, including an archaic route through the olfactory system that predates neocortical expansion by three hundred million years. This olfactory CSF conduit (OCC) runs from the medial temporal lobe (MTL) along the lateral olfactory stria, through the olfactory trigone, and down the olfactory tract to the olfactory bulb, where CSF seeps through the cribriform plate to the nasal submucosa. Olfactory dysfunction is common in AD and could be related to alterations in CSF flow along the OCC. Further, reductions in OCC flow may impact CSF hydrodynamics upstream in the MTL and basal forebrain, resulting in less efficient Abeta removal from those areas-among the first affected by neuritic plaques in AD. Factors that reduce CSF drainage across the cribriform plate and slow the clearance of metabolite-laden CSF could include aging-related bone changes, head trauma, inflammation of the nasal epithelium, and toxins that affect olfactory neuron survival and renewal, as well as vascular effects related to diabetes, obesity, and atherosclerosis-all of which have been linked to AD risk. Problems with CSF-mediated clearance could also provide a link between these seemingly disparate factors and familial AD mutations that induce plaque and tangle formation. I hypothesize that disruptions of CSF flow across the cribriform plate are important early events in AD, and I propose that restoring this flow will enhance the drainage of Abeta oligomers and other metabolites from the MTL.

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